THE REMARKS

Amendments

In the interest of expediting the issuance of allowable claims, Applicant amends Claims 92-98, 100-102, 105, 107-115, 116-118, 122, 124 and 125 in order to reduce and clarify the issues. Applicant reserves the right to reintroduce these claims in one or more continuation type application(s).

Claims 92, 105, 109 and 122 are amended to delete the recitation "a nucleic acid that comprises" or "nucleic acid". Support for this amendment is found, for example, in page 2, line 36.

Claims 92-98, 100, 105, 107-115, 117, 122, 124 and 125 are amended to recite "antisense oligonucleotide". Support for this amendment is found, for example, in page 2, line 36.

Claims 92-95, and 109-112 are amended to replace the phrase "up to about []% adenosine" with "less than []% adenosine". Support for this amendment is found, for example, in page 14, lines 2-4.

Claims 92-95, 101, 109-112 and 118 are amended to delete the term "about". Support for this amendment is found, for example, in page 300, lines 32-37.

Applicant respectfully contends that the amendments will place the case in condition for allowance. No new matter is added in any of the above amendments and the Examiner is respectfully requested to enter the amendments and reconsider the application.

Interview with Examiner on November 19, 2003

Applicant acknowledges with thanks the interview with Examiners Janet L. Epps-Ford and Andrew Wang on November 19, 2003. During the interview, the Examiner and Applicant's representative, Mr. Albert P. Halluin, discussed Claims 92-125. The Examiner has raised the issues of a potential rejection under 35 U.S.C. § 112, first paragraph (i.e., over lack of enablement) and a potential rejection under 35 U.S.C. § 102/103 over cited references found in an additional search that the Examiner had done. Specifically, the references cited were U.S. Patent Nos. 6,001,644 and 6,207,646. Mr. Halluin proposed formally requesting the amendment of the claims as submitted in the present Supplemental Amendment, and the submission of an executed declaration by Dr. Cynthia B. Robinson to address the enablement issue and the unexpected properties of the claimed antisense oligonucleotides in small particle size for treating respiratory diseases and disorders. The

Robinson Declaration includes information regarding the novel delivery of the antisense oligonucleotides in a concentrated and localized manner to the respiratory system of a subject for treatment of diseases associated with the respiratory tract. The Examiners have indicated they would consider these documents when they are filed.

Enablement issue

Applicant respectfully asserts that the Claims 92-125 are fully enabled by the teachings of the specification. Applicant submits a signed declaration by Dr. Cynthia B. Robinson to demonstrate that antisense oligonucleotides that are complementary to genes other than an adenosine receptor are also effective in reducing expression of these genes thereby treating a pulmonary disease. The Robinson Declaration provides data to show that oligonucleotides that are antisense to bradykinin B2 receptor, eotaxin and interleukin 4 and 9 receptors, are effective for treating a respiratory disease or disorder. This information was in the specification as filed. Therefore the specification enables an in vivo method of delivering a pharmaceutical composition to a target polynucleotide comprising administering to the airways of a subject an antisense oligonucleotide in a pharmaceutical composition of particle size of 0.5 μm to 10 μm in size or 10 μm to 500 μm in size.

Prior art issues

Applicant respectfully asserts that the Claims 92-125 are novel and non-obvious over all cited prior art references.

It is recognized that a claim for a known substance which differs from the prior art only in degree, as for example in size or form, may not be patentable. An exception to this view has been made when a compound or composition possesses a specific activity that is greater than a prior art compound or composition and such was unpredictable from the prior art, then the compound or composition has been found patentable. The courts have looked for significant, advantageous unexpected differences. *In re Lunsford*, 148 U.S.P.Q. 716 (CCPA 1966). The court stated that "in all section 103 cases, we must look first to the *differences* between the prior art and the subject matter sought to be patented and then determine if what appellant did, or made, *as a whole*, would have been obvious." *Id.* at 720 (emphasis in the original).

Factors to be considered in determining whether an old product in a new form is obvious

over the prior art include (1) whether the claimed chemical compound or composition has the same utility as closely related materials in the prior art, and (2) whether the prior art suggests the particular form or structure of the claimed material or suitable methods of obtaining that form or structure. *In re Cofer*, 148 U.S.P.Q. 268 (CCPA 1966) (claims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals).

Applicant respectfully asserts that the use of antisense oligonucleotides in the small particle form is novel and non-obvious in that the administration of antisense oligonucleotides in the small particle form to a subject's lungs provides for unexpectedly superior results of efficacy. The Robinson Declaration shows that the claimed methods of treatment using antisense oligonucleotides in small particle sizes and the claimed pharmaceutical compositions of antisense oligonucleotides in small particle sizes provides superior results in treating respiratory diseases and disorders. The treatment of diseases by use of antisense oligonucleotides has the potential of being administered in a variety of means. Typically, such administration is in the form of injection, as this mode of administration has been used by investigators for treatment of diseases using antisense oligonucleotides. This mode of administration permits controlled administration of the drug and potential systemic treatment of a target disease. However, recent studies (subsequent to the effective filing date of the present invention) have shown that injection or oral administration of drugs to treat respiratory diseases such as asthma have not been effective (e.g., use of dehydroepiandrosterone for the treatment of asthma). Direct administration of drugs to the airways may be problematical in controlling the dosage and proper adsorption of the drug at the site. The results obtained using the present invention show the superiority of treating respiratory diseases by controlling the particle size of the drug and administering the drug directly to the airway of the patient over the systemic treatment. The Robinson Declaration shows that the claimed invention provides superior results of efficacy as compared to the results one would expect if the oral or injectable treatment were used. Specifically, by providing small particle size of 1-5 μm for small airway deposition or 0.5 μm to 500 μm for upper airway deposition one is able to achieve a higher concentration of the antisense oligonucleotide drug at the specific locality where it is to interact with its target polynucleotides. The cited prior art neither teaches nor suggests such advantages.

U.S. 6,001,644

Based on the telephone conversation with the Examiner on November 17, 2003, the Examiner has brought to the Applicant's attention: U.S. Patent No. 6,001,644 (hereafter the '644 patent). Applicant respectfully asserts that the '644 patent neither anticipates nor renders obvious the claimed invention. The '644 patent discloses a method for treating cystic fibrosis by introducing a construct into the lung cells of a mammal and expressing a nucleic acid from the construct in the lungs of the mammal, wherein the nucleic acid may be an antisense strand of DNA (col. 4, lines 17-32).

The disclosure of the '644 patent neither anticipates nor renders obvious the claimed invention for the following five reasons:

1) The '644 patent discloses a method whereby a construct is administered to a mammal and the construct expresses an antisense strand DNA in the lung. The present claimed invention is directed a method whereby the antisense oligonucleotide itself is administered into the lung, and a pharmaceutical composition comprising an antisense oligonucleotide, i.e. the antisense oligonucleotide is not expressed in the cells of the patient.

2) The '644 patent discloses a method for increasing the expression of a gene, specifically the gene encoding the CFTR protein. The present claimed invention is directed a method and a pharmaceutical composition for reducing the expression of a gene.

3) Besides "a defective or mutant CFTR gene" (col. 27, lines 51-54), the '644 patent does not disclose the specific target gene that an antisense strand DNA is to target. The present claimed invention is directed a method and a pharmaceutical composition whereby the antisense oligonucleotide targets a polynucleotide that results in alleviating hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy. Specifically, the present application provides a list of more than 160 proteins involved in a pulmonary disease or condition (pages 9-10). The genes encoding these proteins are targets for the claimed antisense oligonucleotides. In addition, the genes are neither defective nor mutant.

4) The '644 patent does not disclose an antisense oligonucletide that comprises 15% or less adenosine.

5) The '644 patent is not enabling for a method of administering small particle size antisense DNA into the lungs for treating a lung disease or disorder. In contrast to the present

application, the '644 patent does not provide any experimental data to demonstrate the efficacy of alleviating a lung disease or disorder by administering a small particle size to a patient.

Further the '644 patent does not render the claimed invention obvious, because one of ordinary skill in the art relying on the '644 would have not a reasonable expectation of success in treating a lung disease or disorder by administering an antisense oligonucleotide of a small particle size comprising 15% or less adenosine.

U.S. 6,207,646

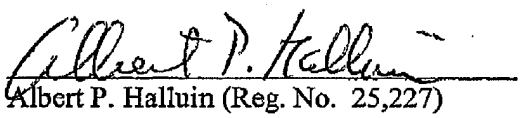
The Examiner has also brought to the Applicant's attention: U.S. Patent No. 6,207,646 (hereafter the '646 patent). Applicant respectfully asserts that the '646 patent neither anticipates nor renders obvious the claimed invention. The '646 patent discloses using immunostimulatory oligonucleotides containing CpG unmethylated dinucleotides to redirect a Th2 response to a Th1 response. The '646 patent discloses examples using such oligonucleotides in cell cultures (for example, col. 39-41, Example 10) and also by **injection** of such oligonucleotides into mice to prevent development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma (col. 42, Example 12). The '646 patent discloses not disclose the use of any antisense oligonucleotide. Further, the '646 patent teaches away for the claimed invention because the '646 patent discloses administering the oligonucleotides by injection. Therefore, the '646 patent does not render the claimed invention obvious, because one of ordinary skill in the art relying on the '644 would have not a reasonable expectation of success in treating a lung disease or disorder by administering an antisense oligonucleotide of a small particle size comprising 15% or less adenosine.

CONCLUSION

Applicant believes that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109.

Respectfully submitted,

Date: November 24, 2003



Albert P. Halluin (Reg. No. 25,227)
Robin C. Chiang (Reg. No. 46,619)

HOWREY SIMON ARNOLD & WHITE, LLP
301 Ravenswood Avenue
Box 34
Menlo Park, CA 94025
(650) 463-8109